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ORIGINAL ARTICLE

A dedicated Fracture Liaison Service telephone program and use of bone turnover markers for evaluating 1-year persistence with oral bisphosphonates

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Abstract

Summary Telephone call intervention did not improve alendronate persistence in Fracture Liaison Service (FLS) patients in this study. A bone turnover marker cut-off point for alendronate persistence is proposed for individual FLS patients.

Introduction FLS aims to prevent subsequent fractures, which should include improving patients' persistence with prescribed oral bisphosphonates. We studied the influence of telephone calls and the predictive value of changes in bone turnover markers (BTMs) for evaluating persistence with alendronate.

Methods Postmenopausal women with a recent fracture and osteoporosis who started alendronate were randomized to receive three phone calls (PC) (after 1, 4, and 12 months) or no phone calls (no PC). s-CTX and P1NP were measured at baseline and after 3, 6, 9, and 12 months. As a reference group, 30 postmenopausal osteopenic patients with a recent fracture were analyzed as well. Persistence was assessed using the Dutch National Switch Point Pharmacies-GPs database and cross-referenced with PC, no PC, and BTM changes. Cut-off values of BTMs were calculated based on least significant change (LSC) and also on underrunning median values of the untreated osteopenic postmenopausal reference group with a recent fracture.

Results Out of 119 patients, 93 (78%) completed 12 months follow-up (45 PC and 48 no PC). Mean age was 69 years. Persistence was similar in PC and no PC participants. The cut-off value > 29% (< 415 ng/L) as LSC of s-CTX and > 36% (< 53.1 μg/L) as LSC of P1NP was determined optimally showing alendronate persistence after 1 year (being 93 and 88%, respectively).

Conclusions In this context, telephone calls did not improve persistence. In around 90% of patients, 1-year alendronate persistence was confirmed by achieving LSC of s-CTX and of P1NP at 12 months.

Keywords alendronate · capture the Fracture® Best Practice Framework · Medication dispensation · P1NP · pharmacy deliveries · s-CTX

Introduction

The Fracture Liaison Service (FLS) is advocated as the most appropriate approach for secondary fracture prevention in patients with osteoporosis [1, 2]. Besides successful prevention of subsequent fractures, FLS activities have been shown to reduce mortality [3]. The FLS concept and its necessity were first reported by the Glasgow group [4, 5]. The concept

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includes full diagnostic evaluation with a focus on detecting underlying disorders and determining the appropriate tailor-made treatment. The International Osteoporosis Foundation (IOF) introduced the Capture The Fracture® (CtF) Best Practice Framework (BPF), which consists of 13 standards for evaluating the performance of any FLS, however not including telephone intervention nor taking lab samples for bone turnover markers (BTMs) [6]. The current study pertains to BPF standard 12, i.e., to ascertain what processes are in place to ensure that long-term management of fracture risk is reliably provided [6].

Recently, inventories on CtF criteria analyzed FLS qualities worldwide [7–9], and our own group reported nationwide on 24,418 Dutch patients [10]. The principal weakness was an FLS attendance of 49% [10]. Notably, all recent fracture patients older than 50 received invitations for follow-up in line with the Dutch Guideline on Osteoporosis and Falls [11]. Besides low numbers of patients attending, a second concern is the low persistence with treatments. In the Netherlands, a nationwide survey of medication dispensation showed up to 40% persistence for anti-osteoporosis medication during 12 months [12]. These findings were obtained from the medication dispensation database on osteoporosis medication, which was generated by IMS Health based on Dutch nationwide data of most pharmacies' sales to patients. Contrarily, a recent study indicated a much higher persistence of 75% in patients with a recent fracture [13]. Therefore, we hypothesized that persistence in recently fractured patients may be improved by means of telephone calls during the first year of follow-up. Telephone initiatives to improve persistence with bisphosphonates have been tested previously, yet not in patients attending FLS [14–26] (Table 1).

In this study, the primary objective was to compare the effect of a dedicated telephone call intervention with standard FLS care on persistence with bisphosphonates at 12 months. The secondary objective was to analyze if BTMs are markers of persistence verified by pharmacy deliveries in LSP.

Patients and methods

Study procedure

Consecutive female patients who attended the FLS due to a recent non-vertebral or clinical vertebral fracture were included if they were 50 years or older. In each patient, treatment was initiated in line with the Dutch Guideline on Osteoporosis and Falls [11]. This guideline recommends treatment in case of a T-score of − 2.5*SD or less, or a T-score between − 1.0 and 2.5*SD and prevalent vertebral fractures on Vertebral Fracture Assessment (VFA). Patients were excluded in case of metabolic bone disorders. Vitamin D deficiency without secondary hyperparathyroidism was not an exclusion criterion.

All patients with osteoporosis and osteopenia received FLS standard care, including lifestyle and nutrition education according to the Dutch National Guideline [11]. Patients with vitamin D deficiency (< 50 nmol/l) were prescribed a daily dose of calcium (500 mg) and vitamin D3 (800 IU) [11]. Each patient received alendronate 70 mg once weekly. After obtaining informed consent, patients who agreed to participate in the study were randomized to either phone call (PC) intervention or no phone calls (no PC). Besides, we selected a reference group of 30 postmenopausal osteopenic patients with a recent fracture to observe the course of BTMs during fracture repair. In all patients in the randomized groups and in the reference group, blood was drawn for BTM assessment at study start and after 3, 6, 9, and 12 months. Patients in the PC group were called after 1, 4, and 12 months. All telephone calls were made by the same experienced FLS nurse. These calls were particularly meant to remind patients not to forget medication and to exchange views about side effects. In case of clear evidence of drug intolerance, patients were withdrawn from the study and alternative treatments were offered.

Bone density measurement and VFA

A patient was diagnosed with osteoporosis if she fulfilled the WHO criteria for osteoporosis (a T-score of ≤ − 2.5SD at the total hip, femoral neck, or lumbar spine) or if she had at least one vertebral fracture and a loss of height of more than 25% on radiography or of more than 40% on VFA, according to Genant's classification [27]. Criteria for osteopenia were a T-score between − 1.0 and − 2.5SD at the lumbar spine and/or hip and no morphometric abnormalities (Hologic DXA equipment, Hologic Discovery QDR Series).

Bone turnover markers

P1NP was measured by means of radioimmunoassay (RIA; Orion Diagnostica, Espoo, Finland) and s-CTX by means of electrochemiluminescence immunoassay (ECLIA; Elecsys 2010 Roche Mannheim, Germany). Fasting serum samples were stored frozen at − 20 °C within 1 h after blood sampling until analysis. P1NP and s-CTX were assayed and expressed in concentrations and in z-scores, using a Dutch Reference Values Group (350 women older than 50) [28]. Blood collection took place at baseline (study start) and after 3, 6, 9, and 12 months, and all samples were finally sent off as one batch for analysis at the laboratory of the University Medical Centre, Groningen, the Netherlands.

Table 1 Studies on interventions with phone calls

Study	Design	Country	Setting	Number of participants	Description of the study	Study flow	Results
Clowes 2004 [14]	RCT	UK	Osteoporosis clinic	Intervention	Arm A: 24 Arm B: 25	Arm A: Patients met with nursing staff at 12, 24, and 36 weeks and participated in pre-defined interviews consisting of open questions related to well-being and medication problems Arm B: Same as Arm A except following each interview, patients were also presented with a graph showing their response to therapy based on BTM measurements	Positive. Survival analysis showed that the monitored group increased cumulative adherence to therapy by 57% compared with no monitoring. There was a trend for the monitored group to persist with therapy for 25% longer compared with no monitoring. Marker measurements did not improve adherence or persistence to therapy compared with nurse monitoring alone
				Control Control	24 269	Usual care	
Shousboe 2005 [15]	RCT	USA	Clinic/telephone	Intervention	37	Patients received an osteoporosis informational brochure, BMD test, and four telephone consultations with a nurse educator	Negative result nurse group versus usual care
				Control	31	Patients received an osteoporosis informational brochure	
Cooper 2006 [16]	RCT	UK	Physicians' offices	Intervention	547	Monthly ibandronate tablet (150 mg) and a patient support program that included information about osteoporosis; monthly reminder phone calls from nurses who provided dosing instructions and osteoporosis information and who stressed the importance of adherence; and a newsletter at 3 months	Positive. The PERSIST study demonstrated that persistence with treatment was increased in patients receiving once-monthly ibandronate plus patient support compared with once-weekly alendronate
				Control	529	Patients met with a physician (no leaflet provided)	
Delmas 2007 [17]	RCT	Multi-national	Hospital-based and academic clinics	Intervention	1189	Same as control except patients also received feedback on their response to therapy based on BTM measurements at weeks 13 and 25	Negative. Persistence assessed with electronic drug monitors was measured. Compared with an intervention based on a good BTMs response, result was associated with a significant improvement in persistence. Persistence was unchanged or lower when reinforcement was based on a stable or poor BTM response respectively
				Control	1113	Patients received calcium, vitamin D, and risedronate (5 mg) with instructions for taking the medication. At weeks 13 and 25, patients received information about the importance of adherence with therapy	
Cook 2007 [18]	NRNCT	US	Clinic/telephone	Intervention	188	Patients received phone calls from nurse educators who provided counseling consistent with motivational interviewing principles	Positive. 6-month adherence based on pharmacy and clinical interview data was significantly higher than the general population rate. A comparison with nonparticipants approached significance,
				Control	529 (NR)		

Table 1 (continued)

Study	Design	Country	Setting	Number of participants	Description of the study	Study flow	Results
						National baseline data on osteoporosis medication adherence was used. Patients received weekly alendronate 70 mg	and there was a significant dose-response effect. The results support the use of psychological techniques to improve adherence and the use of telehealth to disseminate evidence-based patient counseling
Shu 2009 [19]	RCT	US	Physicians' offices/telephone/-mail	Intervention	80	Patients received a letter with osteoporosis information and an automated phone call inviting them for a BMD test. Their physicians received osteoporosis education	Negative. The educational intervention did not significantly improve medication compliance or persistence with osteoporosis drugs
				Control	46	Usual care	
Waalen 2009 [20]	RCT	USA	Telephone calls	Intervention	109	Women in the telephone-based osteoporosis group were monthly reminded by telephone to collect medication	Positive. Of 109 women in the telephone-based osteoporosis clinic group, 75 (68.8%) were using osteoporosis medication at 1 year compared with 46 of 102 women (45.1%) in the usual care group ($p < .001$). The use of osteoporosis medication may be significantly improved via a monthly telephone follow-up
				Control	102	Usual care	
Solomon 2010 [21]	RCT	USA	Motivational telephone counseling	Intervention	1046	OPTIMA study. Telephone-based counseling	Borderline positive. No statistically significant improvement was found in adherence to an osteoporosis medication regimen using a telephone-based motivational interviewing intervention
				Control	1041	Usual care plus educational mails	
Tamone 2012 [22]	NRCT	Italy	Telephone calls	Intervention	382	Patients starting with teriparatide received 1 phone call per week during the first month, then 1 phone call per month and per 3 months during the following 5 and 12 months	Borderline positive. The persistence rate of the group following the program was 85.6%, 8.2% higher than that of the group not following any program (77.4%).
				Historical	398	Historical cohort	Discontinuation in the follow-up program group occurred mainly at early stages of the treatment due to adverse events
Stuurman-Bieze 2014 [23]	RCT	Netherlands	Pharmacy initiative	Intervention	495	MeMO intervention. Continuous monitoring of chronic drug use. Tailored pharmacy counseling and interventions	Positive. Pharmacists can decrease nonadherence to osteoporosis medication, via continuous monitoring and tailored counseling sessions. In the usual care group, 32.8% of patients initiating osteoporosis medication discontinued or were non-adherent, compared to 19.0% of patients in the intervention group
				Control	442	Usual care	

Table 1 (continued)

Study	Design	Country	Setting	Number of participants	Description of the study	Study flow	Results
Bianchi 2015 [24]	RCT	Italy	Telephone calls	Intervention	Arm 1: 110 Arm 2: 111	Intervention group Arm 1 received information materials and intervention group Arm 2 received the same information plus 3-monthly telephone calls	Negative. Additional interventions during the follow-up, including costly interventions such as phone calls and educational meetings, did not provide significant advantages. The special effort of devising and providing additional reminders did not prove effectiveness
				Control	113	Usual care.	

Evaluation of persistence with alendronate based on the Dutch National Exchange Point Pharmacies-GPs (LSP)

After study completion, dispensation data of all participants were collected from the Dutch Landelijk Schakel Punt (LSP), translated in English as National Exchange Point Pharmacies-GPs [29] after verifying whether each patient had consented to the use of personalized data stored in this database. Since patients in the Netherlands are encouraged to store their identifiable healthcare and pharmacy data in the LSP, this database offers accurate information on prescriptions and data on deliveries, including the name of the pharmacy, the date of prescription, the number of prescribed tablets, the prescriber, and the dosage regimen. Thus far, nationwide, more than 11 million Dutch citizens (which is over 70% of the population) consented to giving access to LSP. Pharmacy staff are legally bound to request informed consent regarding the review of individual dispense data.

Statistics

Data were analyzed using Statgraphics Centurion XVII software (Version 17.1.08 for MS-Windows; Statpoint, Inc., Warrenton, VA, USA).

A power analysis was conducted using G*Power software (Germany, version 3.1) to determine the number of patients needed in this study. Two groups of women would have bisphosphonates prescribed. Sample sizes per group were estimated a priori for two-sided significance level alpha = .05 and power = 80% using Fisher's exact test for unequal proportions in two independent groups. Proportions of patients (= % medication compliant) with phone calls versus no phone calls were compared in the analysis: the first proportion was 40% (no phone calls) and the second proportion was 70% (phone calls). Compliancy was scored by calculating the biologically and statistically significant decrease (so-called least significant change) in the two serum BTMs. The output indicated that 42 patients would be needed in each group to have a power of 80%. These numbers were corrected by 15% both for non-parametric statistical tests and losts to follow-up: the final numbers of patients estimated were (rounded up) 50 per group.

Comparison of phone call (PC) versus no phone call (no PC) intervention effects on persistence

We used a logistic regression model comparing the binominal variable intervention (PC = 1; no PC = 0) and persistence with alendronate at 12 months (LSP Yes vs. No) as a binary outcome variable. Besides least significant change (LSC), other censors were studied using data from the reference group after showing statistical feasibility of pooling. The outcomes of LSC and censors applied in our FLS patients were compared to the LSC criterion proposed by the IOF/ECTS Working Group [30]. BTM levels and both the age- and gender-adjusted near-Gaussian z-scores were analyzed. BTMs and LSP results were analyzed separately according to time since fracture, study start, and a fixed time of 180 days (as time outcome variables). For this, linear models were used analyzing BTMs at various time points with the fracture codes as categorical factors. Since the outcomes at these various time points were similar, we only report those at 180 days after fracture (see Fig. 2). Measuring data of the reference group were repeated at the various time points and pooled for further analysis. Statistical changes between the BTM level or z-score at study start before treatment and after alendronate treatment were analyzed in order to find medication-compliant BTM measures in accordance with LSP Yes or No. The binominal censors explored were LSC, underrunning the median estimates (< median; abbr. MedREF) from the pooled BTM levels of the reference group as previously described [31] and underrunning the calculated outcome BTM level of the median after correction for outliers (< median absolute deviation; abbr. MedMAD) [32]. Since near-Gaussian distribution was observed and tested for the BTM levels of the reference group

at the various points in time, we applied a consistency factor of 1.4826. For this study, we used LSCs (95% confidence, two-sided) as previously reported for another Dutch cohort, i.e., z-scores of 36% for P1NP and 29% for s-CTX [33]. Logistic regression was applied to estimate odds ratios and their 95% confidence intervals, using completed medication dispensation at 12 months (LSP Yes or No) and BTMs and PC and no PC and the separate persistence parameter for both P1NP and s-CTX (Yes = 1; No = 0) and fractures. Where applicable, a p value of < .05 was considered statistically significant at the 95% confidence level.

Ethics

The study with number NL 35164.098.11 was approved by the regional Medical Ethical Review Board (METC Zuidwest Holland) and was carried out in accordance with the declaration of Helsinki and the guidelines of the International Conference on Harmonization Good Clinical Practice (GCP). Written informed consent was obtained from all participants included in the study and in the reference group.

Results

From June 2012 to January 2014, 881 postmenopausal women that attended the FLS of the Reinier de Graaf Gasthuis, Delft, the Netherlands, were evaluated: 350 (40%) with osteoporosis, 399 (45%) with osteopenia, and 132 (15%) with a normal T-score. Of the 350 osteoporotic patients, 119 (34%; mean age 69.5 years (range 53–86)) consented to participate in our telephone intervention study. After withdrawal for several reasons, 45 completed the study in the PC group and 48 in the no PC group. Obviously, reasons for dropping out were known in the PC group (12 patients dropped out for GI reasons and 3 patients dropped out for motivational issues). In each case, dropping out did occur within the first 4 months of the study based on self-reporting. Other non-oral osteoporosis treatments were offered and accepted by six patients. In the no PC group, dropping out was registered in LSP at 12 months (LSP does not include documentation about the cases who dropped out from the study). Subsequently, none of these patients received other osteoporosis medication.

Of 30 osteopenic reference group patients, 23 gave the adequate number of blood samples according to study protocol, see Fig. 1. Baseline characteristics of all participants are listed in Table 2.

PC versus no PC

Censors indicate significant bisphosphonate-induced lowering of the respective BTMs and were described as proportions at each point in time using intention-to-treat (ITT) ($n = 119$) and per-protocol (PP) ($n = 93$) analyses. LSP analysis according to ITT revealed LSP PC—71.2% and no PC—67.9% ($p > 0.05$).

Moreover, 93 patients who completed the study (PP) also showed no significant difference in LSP between the PC group and the no PC group (PC 75% and no PC 76%, $p > 0.05$).

Bone turnover markers and LSP

Logistic regression using the binominal variable intervention PC and no PC disclosed no significant relationship between intervention and LSP Yes or No, thus allowing data from both

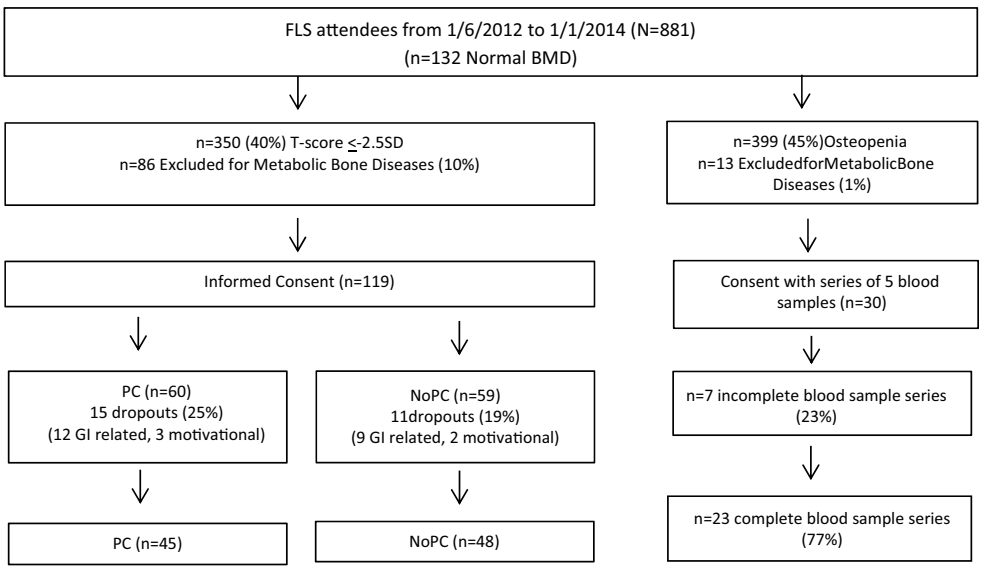

Fig. 1 Study flowchart

Table 2 Baseline characteristics of reference and study groups

Baseline characteristics $N = 93$	RCT group	Phone calls group	No phone calls group	Reference group
Per-protocol analysis	$N = 93$	$n = 45$ (48%)	$n = 48$ (52%)	$n = 23$
Age: years (mean); distribution	69.5; 53–86	67.9; 55–78	69.4; 53–86	60.2; 51–74
Hip fracture; number (%)	7 (7%)	5 (11%)	2 (4%)	1 (4%)
Vertebral fracture; number (%)	6 (6%)	2 (4%)	4 (8%)	–
Major fracture; number (%)	41 (44%)	21 (47%)	20 (42%)	6 (26%)
Minor fracture; number (%)	39 (43%)	17 (38%)	22 (46%)	16 (70%)
DEXA T-score hip: mean (*SD); distribution (*SD)	− 2.2; − 0.3 to − 4.2	− 2.5; − 1.5 to − 4.2	− 2.0; − 0.3 to − 3.7	− 1.7; − 0.4 to − 2.4
DEXA T-score lumbar spine mean (*SD); distribution (*SD)	− 2.1; + 0.3 to − 4.3	− 2.4; − 0.5 to − 4.2	− 1.9; + 0.3 to − 4.3	− 1.3; − 0.3 to − 2.5
VFA: number of prevalent vertebral loss of height > 40% (%)	15 (16%)	4 (8%)	11 (23%)	–

T-hip scores, T-lumbar spine scores, and VFA measures from the PC and no PC groups did not show a near-Gaussian distribution. After checking for equal distributions using the Kolmogorov-Smirnov test, the medians of the variables mentioned were compared applying both the non-parametric Wilcoxon-Mann-Whitney test and Notched Box-and-Whisker plots. We found no significant differences in T-hip, T-lumbar spine, and VFA between PC and no PC groups

interventions to be combined ($n = 93$). In this group analysis, we found an LSP Yes in more than 85% (range 85–94) of those patients who had a P1NP decrease of more than 36% LSC and an LSP Yes in nearly 100% of those who had an s-CTX decrease of more than 29% LSC. Looking for a single optimal BTM for persistence prediction, we compared previously reported LSCs and two other censors: median of reference group (MedREF) and median absolute deviation of reference group (MedMAD). (see Table 3).

Listed data represent optimal LSC cut-off values for alendronate persistence at 12 months according to LSP for P1NP and s-CTX. The outcomes P1NP and s-CTX levels were expressed as identifiable patient numbers (Yes/No). Censors were expressed at 3 and 12 months after study start. Besides the data obtained in the current study, IOF recommended cut-off values were also listed (see Table 3) [30, 34]. The results for P1NP and s-CTX at 3, 6, and 9 months are comparable with the 12-month results (data not shown).

Table 3 BTM compliance outcomes at 3 and 12 months

3 months versus baseline Available BTMs in 86/93 patients (92%) $n = 7$ LSP = 0 (8%) $n = 86$ LSP = 1 (92%)	P1NP[1] LSC => 3-6%	s-CTX[1] LSC => 2-9%	P1NP < 53.1 μg/L MedREF[2]	s-CTX < 415 ng/L MedREF[2]	P1NP < 30 μg/L MedMAD[3]	s-CTX < 233 ng/L MedMAD[3]	P1NP[4] LSC => 38% (IOF)	s-CTX[4] LSC => 56% (IOF)
Non-agreement	13 (15%)	6 (7%)	10 (12%)	4 (4%)	50 (58%)	22 (25%)	16 (19%)	23 (27%)
Agreement	73 (85%)	80 (93%)	76 (88%)	82 (96%)	36 (42%)	64 (75%)	70 (81%)	63 (73%)
12 months versus baseline Available BTMs in 65/93 patients (70%) $n = 26$ LSP = 0 (28%) $n = 67$ LSP = 1 (72%)	P1NP[1] => 3-6%	s-CTX[1] => 2-9%	P1NP < 53.1 μg/L MedREF[2]	s-CTX < 415 ng/L MedREF[2]	P1NP < 30 μg /L MedMAD[3]	s-CTX < 233 ng/L MedMAD[3]	P1NP[4] => 38% (IOF)	s-CTX[4] => 56% (IOF)
Non-agreement	6 (9%)	4 (6%)	2 (3%)	1 (2%)	12 (19%)	11 (17%)	6 (9%)	15 (22%)
Agreement	60 (91%)	60 (94%)	62(97%)	63 (98%)	52 (81%)	53 (83%)	60 (91%)	52 (78%)

[1] Defined as the least amount of change between measurements over time that must be exceeded before a change can be considered true (with a certain confidence 2.77) in an individual

[2] P1NP AND s-CTX values are calculated based on median of pooled reference postmenopausal group data (MedREF)

[3] P1NP and s-CTX values are calculated based on medium of pooled data at time of study start*1.48 median absolute deviation of pooled data at time of study start (MedMAD)

[4] IOF proposed LSC percentages respectively P1NP 38% and s-CTX 56% in cohorts without previous fracture ≤ 3 months

[5] Calculations based on IOF-proposed premenopausal reference values

Using underrunning median values obtained from the reference group led to similar results, but only with use of the MedREF censor.

Discussion

In this study, we found no favorable effects of a dedicated telephone call intervention on standard care regarding persistence with bisphosphonates at 12 months. Note that this study was executed and analyzed within an FLS setting, which to our knowledge has not been studied before. This study as a whole encompasses real-life FLS practice with or without telephone calls and also BTMs for monitoring medication persistence per individual patient.

We were able to study persistence with BTMs for the analysis of identifiable pharmacy deliveries in the early postfracture phase and at 1-year follow-up. BTMs in the first 3 months post fracture are notoriously hard to interpret because of the bias caused by fracture repair in this phase. As we are interested in the effects of treatment in that early postfracture phase, we studied BTMs in the randomized study groups on alendronate and as a surplus in a group of postmenopausal osteopenic women (as a non-treated reference group) reflecting the natural course of BTMs post fracture.

To substantiate BTMs and the pharmacy deliveries in the analysis of individual persistence, we cross-referenced the identifiable patients in our study groups to a Dutch exchange system on pharmacy deliveries (LSP). This system enables the exchange of healthcare data on pharmacy deliveries among authorized healthcare staff. First of all, the LSP system offers an overview of prescribed medication, but secondly, it generates monitoring facilities of persistence, as nationwide more than 11 million Dutch citizens (which is over 70% of the population) consented to giving healthcare staff access to their personal LSP data.

At the end of this study, we found out firstly that telephone support of patients with an alendronate prescription after a recent fracture is not of importance regarding persistence, which was about 75% (after exclusion of 26 patients who stopped taking bisphosphonates due to GI-related complaints or motivational issues) in both the PC and the no PC groups at 1 year. This finding differs entirely from the persistence of 40% that was previously reported by Netelenbos and Geusens [12]. However, their study was based on the general osteoporotic population-based pharmacy deliveries of alendronate and is not a reflection of those patients starting alendronate soon after sustaining a fracture. Moreover, this difference in persistence could also be explained by the less intensive supervision of patients outside the closely monitored conditions of an RCT. Our findings are in line with the persistence of 74 to 88% found in the study on osteoporosis medication and persistence of Klop [13], who provided more differentiated data on persistence, taking a recent fracture into account as a discerning variable.

Although telephone interventions did not influence persistence in our study, an important favorable effect of these phone calls was that patients who stopped taking alendronate were identified at an early stage. Of the patients who recently started taking alendronate and then stopped, the majority reported GI side effects as reason for stopping this medication. Any undetected cessation of alendronate therapy should be considered an FLS failure, which might be prevented by telephone calls at an early stage and offering alternatives, such as liquid or non-oral medication.

Alendronate persistence is crucial in the long-term treatment for osteoporosis patients. Medication persistence in general regarding chronic conditions is reported to be low, and the World Health Organization (WHO) as well as the International Osteoporosis Foundation (IOF) declared the matter of persistence a major challenge to effective long-term management [35]. It is unfortunate that no effects of telephone intervention were confirmed. Finding no effects is, however, in line with other non-FLS initiated studies, see Table 1 [14–26, 34].

Nevertheless, a number of FLS-initiated actions need to be taken to ensure persistence [36]. Firstly, personal encouragement of taking medication should continue shortly after any traumatic and painful event [37]. Secondly, it is important to try and solve the matter of underestimating the impact of sustaining a fracture and the low attendance of FLS patients, as we have shown previously in an FLS questionnaire study [11]. This low attendance at FLSs is a world-wide phenomenon, resulting in a major care gap. This notion was one of the main starting points for the CtF campaign.

For observing persistence after initiating alendronate, BTMs can be used. However, any biomarker used to monitor persistence may be influenced by fracture repair and bone union. Moreover, the effects of fracture repair could last for more than 800 days, as was shown by data of our untreated reference group ((Fig. 2 (2.4 and 2.5)). Therefore, we compared the course of BTMs since fracture, since start of study, and also at 180 days post fracture, based on data of the minimal wash-out period of fracture effects [38, 39]. Notably, the outcomes at the various time points were similar.

Our findings support the results of the previous TRIO study that compared the persistence with several oral bisphosphonates by assessing P1NP and s-CTX and found that the use of BTMs is feasible [36]. In addition, we studied the individual persistence and our study revealed a promising exactness for s-CTX at 3 months. Compared to s-CTX precision, the reliability of P1NP for individual persistence at 12 months is somewhat lower, as is shown in Table 3.

Notably, data of the current study are based on LSP outcomes per identifiable patient, while previous data were reported at group level. In general, persistence indicated via

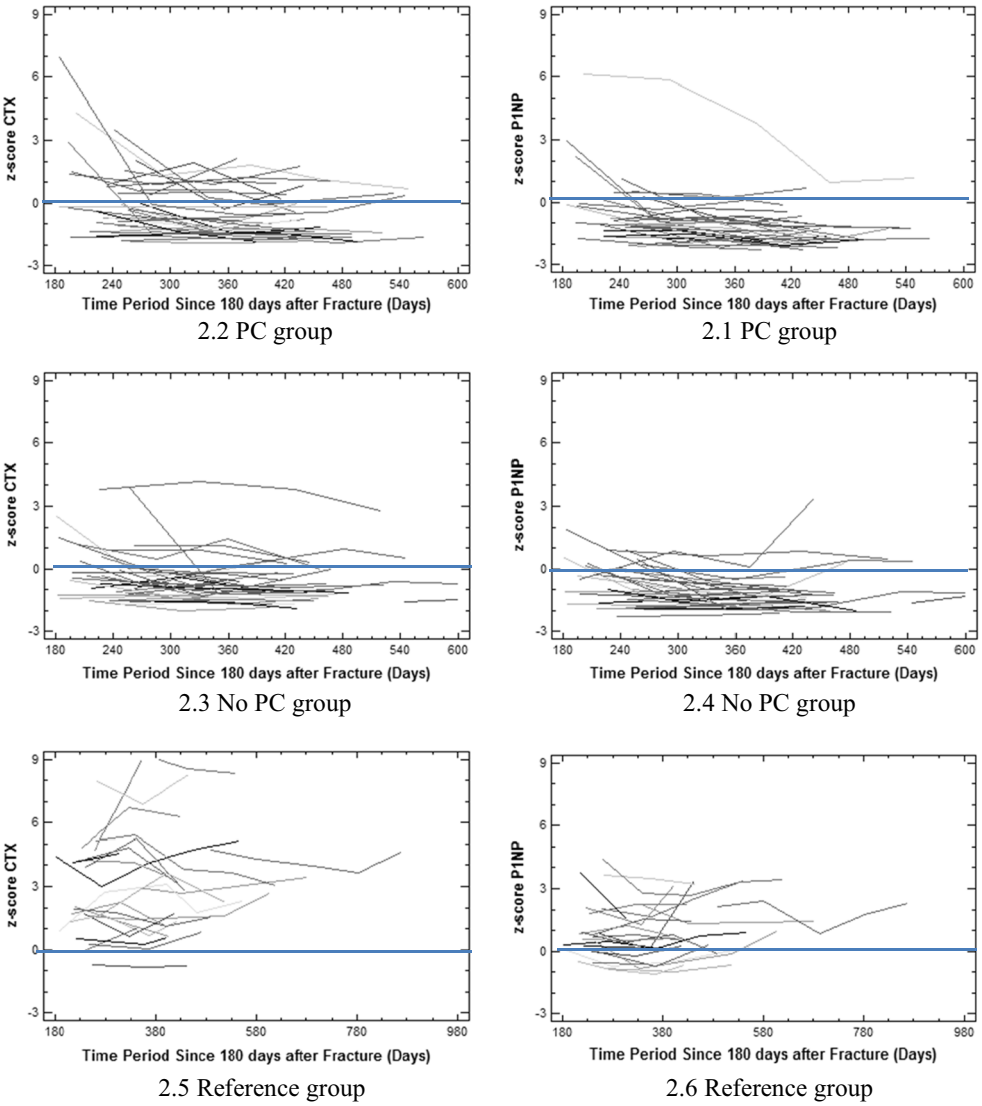

Fig. 2 (2.1–2.6) P1NP and s-CTX z-scores versus time period 180 days post fracture. Scatterplots of P1NP and s-CTX z-scores depicted at 180 days post fracture. Each line represents an individual patient. Data of the PC group and the no PC group on alendronate are depicted in the upper panels (2.1 and 2.2) respectively in the middle panels (2.3 and 2.4). Data of the postmenopausal reference group without alendronate therapy are depicted in the lower panels (2.5 and 2.6), lines at z-score = 0.0 show the mean of the applied parametric 95% reference interval

P1NP and s-CTX agreed fairly well for P1NP, i.e., 36% (current study) versus 38% (TRIO study), but the LSC cut-off point for s-CTX was clearly low in the current study (29 vs. 56% (TRIO study)). Note the importance of the time point at which the BTM samples were taken and of the patient's physical condition at that moment. In our study, blood samples for BTM analysis were taken in recent fracture patients. Our next step was to study individual persistence after correction for outlying data due to biological variations caused by the very long wash-out period of fracture and fracture repair. Besides the median of the reference group (MedREF) to calculate underrunning BTMs on alendronate treatment, we also compared persistence after correction for outliers as calculated with the MedMAD (see statistical paragraph) with most commonly used LSCs. Reference group-derived censors were compared to rule out effects for existing skewness and kurtosis of alendronate BTM suppression and to avoid statistical bias of existing outliers and small sample size. However, use of reference group-derived censors revealed no improvement in the prediction of alendronate persistence.

Several LSC thresholds have been reported using automated and manual assays. Roche Elecsys as used for this study is a commercially available assay and is widely used. Previously reported LSC declines were s-CTX lower than 27% and P1NP lower than 20% [30]. Clearly different LSCs have also been reported for several bisphosphonates, those for alendronate ranging from 38 to 56% [30, 36]. These variations make it questionable whether the percentages reported for the same bisphosphonate can also be ascribed to related factors, for example, retrospective or prospective cohort analysis, ethnicity, or time of fracture repair. Moreover, in previous studies, calculations were based on patients with older osteoporotic fractures [28, 30, 33, 36]. Therefore, we decided to study real-life outcome data from this RCT describing a prospective Dutch FLS treated group shortly after fracture using previously reported Dutch LSC cut-off levels.

In our study, the presumed cut-off values reflecting persistence were rather similar to those reported by Rogers [30], which were 28% for P1NP and 25% for s-CTX versus 36% and 29%, respectively, in our study. Regarding our calculated cut-off values, assessment of s-CTX at 3 months revealed to be best predictive on BTMs for 1-year alendronate persistence. In more detail, in our study, an LSC of s-CTX lower than 29% or a level of less than 415 ng/L (MedREF) at 3 months agreed with nearly all except seven non-delivery cases. By contrast, these s-CTX cut-offs failed in 4 LSP-confirmed deliveries, see Table 3.

Comparing our results with the IOF-proposed LSCs showed less favorable results on pharmacy deliveries. The IOF cut-off levels, however, were not based on osteoporotic women with recent fractures [30, 36].

In comparison to the high agreement regarding LSCs for both the time points 3 and 12 months, similarity in results was found in using the reference group-based censor MedREF (s-CTX < 415 ng/L and P1NP < 53 μg/L); at 3 and 12 months, s-CTX was 96 and 98%, respectively, and P1NP was 76 and 97%, respectively.

By contrast, less agreement was found at 3 months using the reference group-based censor corrected for outliers MedMAD (s-CTX lower than 233 ng/L and P1NP lower than 30 μg/L); this was 75% for s-CTX and 42% for P1NP, respectively, although the difference decreased at 12 months and went up to 83% for s-CTX and 81% for P1NP.

This study has some important limitations. Firstly, the sample size is fairly small but our results on the absence of effects of telephone calls are in our opinion robust and clear. A second limitation is the use of the non-treated reference group, which is small as well, but accepted statistical techniques such as pooling data made the outcome of the reference group useful and valuable, especially for the calculated MedREF and MedMAD besides LSC. Thirdly, a limitation worth mentioning may be the introduction of a potential Hawthorne effect (five blood drawings) towards persistence.

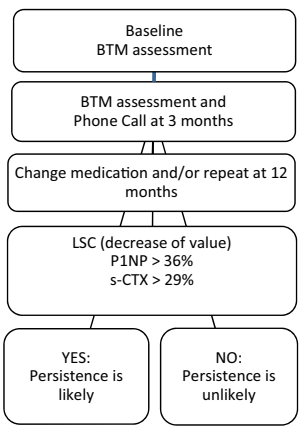

Fig. 3 Algorithm on alendronate persistence follow-up

An important strength of this study was the use of identifiable LSP data, which served as proxy for persistence with any medication, for example, treatment with alendronate.

To conclude, this FLS-initiated study showed an alendronate persistence of 75% after correction for individuals who had to stop taking bisphosphonates. Telephone intervention did not have an add-on effect to alendronate persistence in this study, but offered the advantage of early detection of any reason for stopping medication. LSC, particularly that of s-CTX (compared to baseline BTM level) after early drop out (1 to 3 months), is a practical measure to be used in an FLS real-life situation to analyze persistence with alendronate after 1 year providing use of adequate cut-off points (Fig. 3). The weakness of this study is that outcome results have been reported in a small number of patients. Therefore, more FLS studies are needed to strengthen LSC data while comparing outcomes for different treatments and different populations.

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Compliance with ethical standards

Conflicts of interest None.

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